Complete Summary

GUIDELINE TITLE

Use of 5-alpha-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology-American Urological Association 2008 Clinical Practice Guideline.

BIBLIOGRAPHIC SOURCE(S)

Kramer BS, Hagerty KL, Justman S, Somerfield MR, Albertsen PC, Blot WJ, Ballentine Carter H, Costantino JP, Epstein JI, Godley PA, Harris RP, Wilt TJ, Wittes J, Zon R, Schellhammer P, American Society of Clinical Oncology Health Services Committee, American Urological Association Practice Guidelines Committee. Use of 5-alpha-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. J Clin Oncol 2009 Mar 20;27(9):1502-16. [51 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Prostate cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Treatment

CLINICAL SPECIALTY

Endocrinology
Oncology
Preventive Medicine
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To develop an evidence-based guideline on the use of 5-α-reductase inhibitors (5-ARIs) for prostate cancer chemoprevention

TARGET POPULATION

- Asymptomatic men with a prostate-specific antigen (PSA) $\leq$3.0 ng/mL who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer
- Men who are taking 5-a-reductase inhibitors for benign conditions such as lower urinary tract (obstructive) symptoms

INTERVENTIONS AND PRACTICES CONSIDERED

Use of 5-a-reductase inhibitors (finasteride, dutasteride) for prostate cancer chemoprevention

MAJOR OUTCOMES CONSIDERED

Primary Outcomes

- Prostate cancer incidence or period prevalence, in prostate cancers detected "for cause"
- Distribution of stage of prostate cancer
- Gleason scores
- Incidence or period prevalence of prostate cancer by age, race, baseline prostate specific antigen (PSA) and family history

Secondary Outcomes

- Prostate cancer detected purely for reasons dictated by study protocol, rather than by clinical indication
- Quality of life
- Change in validated urinary symptom scale scores
- Benign prostatic hyperplasia (BPH) progression

- Overall mortality
- Prostate cancer–specific mortality
- Adverse events
- Cost effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The American Urological Association (AUA) commissioned a systematic review of the literature on the role of 5-a-reductase inhibitors (5-ARIs) in the chemoprevention of prostate cancer. That review, which is published in the Cochrane Library, served as the primary source of evidence for this guideline (see "Availability of Companion Documents" field of this summary).

Criteria for Considering Studies for This Review

Types of Studies

For prostate cancer outcomes the reviewers included randomized controlled trials of at least 1 year in duration published after 1984. For non-prostate cancer outcomes, randomized trials were included if: they were at least 6 months in duration published after 1999. This date was chosen because the AUA guideline on the management of benign prostate hyperplasia (BPH) included studies published through 1999.

Types of Participants

Adult men, aged 45 years or older, who are at risk for prostate cancer and have a life expectancy of at least 10 yearsÂ Subgroups of interest include:

- Age: 45-64 years/65-74 years/75 and older
- Race/ethnicity: Caucasian/African-American/Asian/Hispanic/Other
- Baseline prostate specific antigen (PSA) values (ng/mL): 3/ >3-4/>4-10
- Family history of prostate cancer (yes/no)
- Pre-existing BPH (yes/no)
- Pre-existing lower urinary tract symptoms (LUTS) (yes/no)
- AUA/International Prostate Symptom Score (IPSS) Symptom Severity: none to mild/moderate/severe
- Bother/Impact: moderate or greater
- Pre-existing high-grade prostatic intraepithelial neoplasia (PIN) (yes/no)

Types of Interventions

5-ARI (finasteride or dutasteride) versus placebo, no intervention, medical or herbal therapies, or surgical, device/minimally invasive therapies for nonmalignant prostate conditions.

Types of Outcome Measures

The primary outcome was prostate cancer detected "for-cause" period prevalence. For-cause prostate cancers include those that: 1) were suspected clinically during the course of the trial because of symptoms, abnormal digital rectal exam, or abnormal PSA, and were confirmed on biopsy; or 2) during the trial, a recommendation was made for biopsy per the study protocol (e.g., due to increasing PSA) which was never done, and end-of-study biopsy showed prostate cancer; or 3) end-of-study biopsy in the setting of a PSA >4 ng/mL and/or suspicious digital rectal exam (DRE) showed prostate cancer.

Secondary outcomes included: 1) prostate cancers detected due to study protocol rather than clinical indication (see above); 2) overall mortality; and 3) prostate cancer-specific mortality. Reviewers also assessed the clinical benefits of 5-ARI in the treatment of BPH. These outcomes included 1) change in urinary symptom scale scores (IPSS/AUA); 2) BPH progression; 3) development of acute urinary retention; and 4) need for interventions for treatment of LUTS. Reviewers also assessed the harms associated with 5-ARI including 1) impotence/erectile dysfunction; 2) retrograde ejaculation; 3) decreased ejaculate volume; 4) decreased libido; and 5) gynecomastia.

Search Methods for Identification of Studies

MEDLINE and the Cochrane Library were searched through April 2007. Results were supplemented with hand searching of reviews and personal files. The following MeSH terms and text words were used: "finasteride," "dutasteride," "prostatic neoplasms," "azasteroids," "reductase inhibitors" and "enzyme inhibitors." Unpublished information was provided from Prostate Cancer Prevention Trial (PCPT) authors.

NUMBER OF SOURCE DOCUMENTS

Fifteen randomized control trials (RCTs) were identified that met the inclusion criteria; nine of these trials reported prostate cancer period-prevalence.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The American Urological Association (AUA) commissioned a systematic review of the literature on the role of 5-a-redutase inhibitors (5-ARIs) in the chemoprevention of prostate cancer. That review, which is published in the Cochrane Library, served as the primary source of evidence for this guideline (see "Availability of Companion Documents" field of this summary).

Data Collection and Analysis

Trials were categorized as long (>2 year), mid (1 to 2 years) and short (<1 year) term; with trials of at least 1 year duration included for assessment of prostate cancer outcomes. Pooled analyses of outcomes data were conducted using RevMan 4.2 software. Relative risks and absolute risk differences with 95% confidence intervals were calculated for categorical outcomes.Weighted mean differences, the difference between treatment and control pooled means at endpoint, along with 95% confidence intervals were calculated for continuous variables. If heterogeneity was evident between the trials, based on the chi^2 test for heterogeneity ($P < 0.1$) and the I^2 test (>50%), a DerSimonian and Laird random-effects model was utilized, exploration of potential clinical causes of heterogeneity conducted and/or results reported separately. A fixed-effects model was used if heterogeneity criteria were not present. Individual trials outcomes were assessed, with emphasis on the Prostate Cancer Prevention Trial (PCPT) because it was designed to assess whether 5-ARIs prevent or delay prostate cancer.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Panel Composition

The American Society of Clinical Oncology (ASCO) Health Services Committee (HSC) and the American Urological Association (AUA) Practice Guidelines Committee jointly convened an Expert Panel (hereafter referred to as the Panel) consisting of experts in clinical medicine and research methods relevant to chemoprevention for prostate cancer. The experts' fields included medical oncology, urology, pathology, epidemiology, statistics, and health services research. The Panel included academic and community practitioners as well as a patient representative.

Consensus Development Based on Evidence

A steering committee met in October 2005. The steering committee was charged with identifying potential Panel members and with drafting the clinical questions the Panel was to address. In August 2006 the entire Panel met; the Panel completed its additional work through teleconferences. The purposes of the Panel meeting were to refine the questions addressed by the guideline and to make writing assignments for the respective sections. All members of the Panel participated in the preparation of the draft guideline.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Although not specifically within the scope of this document, the Panel did review studies on cost effectiveness. Two analyses have been published on the cost effectiveness of finasteride for prostate cancer prevention using the period prevalence observed in the Prostate Cancer Prevention Trial (PCPT) and making a variety of unverifiable assumptions about the impact of the diagnosed cancers on prostate cancer mortality and the tumor grade-specific lethality of the cancers detected. The results of the cost-effectiveness analyses were highly dependent on assumptions regarding whether the observed increase in high-grade tumors was real or artifactual, and on the cost of drug. The first assumption cannot be tested. Therefore, the Panel concluded that any assessment of cost effectiveness at this point is unreliable and impossible to incorporate into the decision of whether or not to take 5-α-reductase inhibitors for lowering the risk of prostate cancer.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The draft guideline was disseminated for review by the entire Expert Panel. Feedback from external reviewers was also solicited. The American Society of Clinical Oncology (ASCO) Health Services Committee (HSC) and the American Urological Association (AUA) Practice Guidelines Committee, as well as the Board of Directors of both organizations, reviewed and approved the content of the guideline and the manuscript before dissemination.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Should Men Routinely Be Offered a 5-a-Reductase Inhibitor (5-ARI) for the Chemoprevention of Prostate Cancer?

Asymptomatic men with a prostate specific antigen (PSA) $\leq$3.0 who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of the benefits of 5-

ARIs for 7 years for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer) to be able to make a better informed decision. Men who are taking 5-ARIs for benign conditions such as lower urinary tract symptoms (LUTS) would benefit from a similar discussion.

Of note, one Panel member believed that the explanation of decreased prostate cancer period prevalence in the finasteride arm of the Prostate Cancer Prevention Trial (PCPT) is attributable to differential biopsy rates between the two trial arms. The 25% risk reduction is based primarily on the PCPT and the risk reduction of a prostate diagnosis accrued primarily as a result of the lower rates of biopsy among men on finasteride. For those men who underwent a biopsy, the risk reduction was a statistically non significant 10%. By contrast, the principal investigator of the PCPT has published a commentary stating that differential biopsy rate is not likely to account for a substantial proportion of the observed difference. He argues that critics of the PCPT "â□¦ignore the effects of PSA, digital rectal examination (DRE), and biopsy detecting the cancer in the finasteride group, which would be expected to further reduce the risk of cancer overall."

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

For the man who wishes periodic monitoring (opportunistic or organized screening), 5-α-reductase inhibitor therapy during a 7-year period reduces the period prevalence of for-cause cancer diagnoses by approximately 25% (relative risk reduction) for an absolute risk reduction of about 1.4%. Although the majority of the Panel judged that the observed higher incidence of high-grade (Gleason score 8 to 10) cancer in the finasteride group is likely due to confounding factors, the increased incidence of high-grade cancer as a result of induction by the drug cannot be excluded with certainty. Additional benefits accruing from the drug are reduction of the risk of urinary retention and need for surgical intervention.

POTENTIAL HARMS

Adverse events of medication: impotence, retrograde ejaculation, decreased ejaculate volume, decreased libido, gynecomastia

QUALIFYING STATEMENTS

- In formulating recommendations for the use of 5-a-reductase inhibitors (5-ARIs) for prostate cancer prevention, the American Society of Clinical Oncology (ASCO) and American Urology Association (AUA) have considered specific tenets of guideline development, emphasizing review of data from appropriately conducted and analyzed clinical trials. These same tenets can be utilized and applied to formulation of prevention guidelines. However, it is important to note that guidelines cannot always account for individual variation among patients. Guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result.
- ASCO and AUA's practice guidelines and technology assessments reflect expert consensus based on clinical evidence and literature available at the time they are written, and are intended to assist physicians in clinical decision making and identify questions and settings for further research. Due to the rapid flow of scientific information in oncology, new evidence may have emerged since the time a guideline or assessment was submitted for publication. Guidelines and assessments are not continually updated and may not reflect the most recent evidence. Guidelines and assessments cannot account for individual variation among patients, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine the best course of treatment for the patient. Accordingly, adherence to any guideline or assessment is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient´s individual circumstances. ASCO and AUA guidelines and assessments describe the use of procedures and therapies in clinical practice and cannot be assumed to apply to the use of these interventions in the context of clinical trials. ASCO and AUA assume no responsibility for any injury or damage to persons or property arising out of or related to any use of ASCO and AUA's guidelines or assessments, or for any errors or omissions.

Limitations of the Literature

Despite high-quality evidence from randomized trials, the data have limitations. Only one trial reported to date (the Prostate Cancer Prevention Trial [PCPT]) was specifically designed to measure the effect of a 5-ARI on the incidence of prostate cancer; it was not designed with sufficient power to assess the effect of 5-ARIs on the risk of prostate cancer death. To develop a complete assessment of the benefit of 5-ARIs, one would need to know the proportion of cancers finasteride prevents that are truly clinically meaningful. The current literature cannot provide an estimate of this proportion; in particular, data are lacking on clinically meaningful cancers in the age group under consideration (men older than 50 years). A recent analysis of PCPT characterized 34% of cancers as clinically insignificant by histologic criteria, a rate similar to contemporary series of men who undergo treatment. Many cancers prevented by finasteride might never have caused harm, as suggested by the fact that screening leads to substantial

overdiagnosis of nonlethal cancers. Overdiagnosis can increase substantially with a lowering of the prostate-specific antigen (PSA) threshold for prostatic biopsy or an increase in the number of systematic biopsies of the prostate. Overdiagnosis is likely to decrease if ongoing randomized prostate cancer screening trials show a net harm from screening. Therefore, the clinical importance of the prostate cancers diagnosed in existing and ongoing chemoprevention trials is difficult to interpret. The Panel attempted to focus on cancers that were most likely to be of clinical importance (for-cause cancers). One of the most serious limitations in the current literature is the changes that occur in standards for PSA thresholds, criteria for biopsy, and biopsy methods. Continuing changes may alter all evaluations of outcomes.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Personal Digital Assistant (PDA) Downloads
Quick Reference Guides/Physician Guides
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Kramer BS, Hagerty KL, Justman S, Somerfield MR, Albertsen PC, Blot WJ, Ballentine Carter H, Costantino JP, Epstein JI, Godley PA, Harris RP, Wilt TJ, Wittes J, Zon R, Schellhammer P, American Society of Clinical Oncology Health Services Committee, American Urological Association Practice Guidelines Committee. Use of 5-alpha-reductase inhibitors for prostate cancer

chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. J Clin Oncol 2009 Mar 20;27(9):1502-16. [51 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2009 Mar

GUIDELINE DEVELOPER(S)

American Society of Clinical Oncology - Medical Specialty Society
American Urological Association Education and Research, Inc. - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Clinical Oncology

GUIDELINE COMMITTEE

5-α-Reductase Inhibitors Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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Panel Members: Barnett Kramer, MD, *Co-Chair*; Paul Schellhammer, MD, *Co-Chair*; Stewart Justman, PhD, Peter C. Albertsen, MD; William J. Blot, PhD; H. Ballentine Carter, MD; Joseph P. Costantino, PhD; Jonathan I. Epstein, MD; Paul A.Godley, MD, PhD; Russell P. Harris, MD, MPH; Timothy J. Wilt, MD, MPH; Janet Wittes, PhD; Robin Zon, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors in the original journal of publication.

Employment or Leadership Position: None **Consultant or Advisory Role**: Peter C. Albertsen, GlaxoSmithKline (C); Paul A. Godley, GlaxoSmithKline (C); Janet Wittes, Merck (C) **Stock Ownership**: None **Honoraria**: None **Research Funding**: None **Expert Testimony**: None **Other Remuneration**: None

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Society of Clinical Oncology (ASCO) Web site.

Print copies: Available from American Society of Clinical Oncology, Cancer Policy and Clinical Affairs, 1900 Duke Street, Suite 200, Alexandria, VA 22314; E-mail: guidelines@asco.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- 5-alpha-reductase inhibitors for prostate cancer prevention. Companion systematic review. 2008.Â 58 p. Available in Portable Document Format (PDF) from the American Society of Clinical Oncology (ASCO) Web site.
- Discussion guide for doctor and patient. 4 p. Available in Portable Document Format (PDF) from the ASCO Web site.
- Clinical practice guideline on the use of 5-alpha reductase inhibitors for prostate cancer chemoprevention. Slide set. 2007. 25 p. Electronic copies: Available in Portable Document Format (PDF) and PowerPoint from the ASCO Web site.
- Use of 5--reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 clinical practice guideline summary. 2008. 3 p. Electronic copies: Available from the ASCO Web site.

Guidelines are available for Personal Digital Assistant (PDA) download from the ASCO Web site.

PATIENT RESOURCES

The following is available:

- What to know: ASCO's guideline on 5-alpha reductase inhibitors for prostate cancer prevention. 2009. 4 p. Available in Portable Document Format (PDF) from the American Society of Clinical Oncology (ASCO) Web site.

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Date Modified: 3/29/2010


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